

The University of Chicago

CONDENSATIONS BY MEANS OF
HALOGEN ACIDS

A DISSERTATION SUBMITTED TO THE FACULTY
OF THE DIVISION OF THE PHYSICAL SCIENCES
IN CANDIDACY FOR THE DEGREE OF DOCTOR
OF PHILOSOPHY

DEPARTMENT OF CHEMISTRY

1938

By

ATHAN ANASTASOV PANTSIOS

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The author is greatly indebted to Professor M. S. Kharasch for guidance and invaluable advice in the course of this investigation, and to Dr. F. R. Mayo for his constant interest and suggestions.



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INTRODUCTION

The use of halogen acids as condensing agents in organic chemistry has been very limited; whenever these may have been used their function was of secondary nature. In most cases the halogen acids are used in conjunction with the halides of tin, zinc, or aluminum. As a matter of fact, even in these cases mostly hydrochloric acid and only rarely hydrobromic acid have been used, hydriodic acid being ruled out because of its reducing properties and hydrofluoric acid because of the difficulty in working with it.

This work was undertaken in order to establish the use of hydrochloric, hydrobromic, and even hydrofluoric acids as primary condensing agents, particularly in inter- or intra-molecular condensations where water is eliminated in the reaction. It was also intended to demonstrate the usefulness of anhydrous, liquid hydrofluoric acid as a condensing agent due to its great dehydrating power. Particular emphasis was placed upon condensation reaction leading to cyclization.

The extensive use of formaldehyde in most of the condensations studied is justified by the interesting results possible. The Blanc reaction, condensation of formaldehyde with aromatic hydrocarbons in the presence of zinc chloride and hydrochloric acid, is both interesting and useful as the work of Quelet and other investigators seems to indicate.

It is quite difficult to correlate the various phases of the work done since the reactions studied cover a wide field. In many cases neither the reactants nor the products obtained are in any way related. The only integrating factor throughout this work is the use of the halogen acids and in most cases also that of formaldehyde.

It was deemed necessary therefore, because of the lack of a close relationship between the various reactions studied, to divide this work into three distinct parts and to treat each part as an independent unit, both theoretical and experimental considerations included in it.

The first part is concerned with the preparation and the attempted autocondensation of benzylglucamine, having in view the possible formation of isoquinoline-type compounds. No such compounds were obtained even with anhydrous liquid hydrogen fluoride as the condensing agent.

The second part deals with the autocondensation of cyclopentanone, cyclohexanone, 2-ethylcyclopentanone, and 2-methyl-4-isopropylcyclohexanone by means of hydrogen chloride, bromide, and fluoride. Several interesting products were obtained and studied, and at the same time, the importance of substitution in these ketones on the course of the condensation was established. A syn-anti-isomerization was observed in conjunction with some 2,4-dinitrophenylhydrazones of the products and its course studied. An attempt was also made to elucidate the chemical nature of the polymeric resins produced in these condensations.

The third part consists of a series of condensations of several different aromatic nuclei with formaldehyde in the presence of the hydrogen halides. Condensations of nitrobenzene, diphenylmethane, benzene, diphenylamine, and triphenylamine with formaldehyde were attempted and some interesting results obtained.

This work consists of but few examples from the wide field of organic condensations. The results obtained, however, lead to the conclusion that in many of these condensations the more powerful condensing agents, such as sulfuric acid, the metal halides and even sodium ethylate, can be replaced by the halogen acids.

PREPARATION AND AUTOCONDENSATION OF
BENZYLGLUCAMINE

When it was decided to attempt the autocondensation of benzylglucamine, this compound had not (and has not) as yet been described in the literature. A method for its preparation was finally developed. This consisted of the preparation and catalytic reduction of the corresponding Schiff's base, benzalglucamine, since it was not possible to prepare it directly from benzylchloride and glucamine. The preparation of secondary amines by the reduction of the corresponding Schiff's base is a very common method and quite useful in many cases. Several different reduction methods have been employed and are reported in the literature, each one being advantageous for certain of the Schiff's bases but of little value for others. Such reducing agents as sodium,¹ magnesium,² and zinc,³ aluminum amalgam,⁴ electrolysis,⁵ and hydrogenation⁶ have all been used.

The Schiff's bases, even though most of them are well-defined compounds and quite stable thermally,⁷ are very readily hydrolyzed by acids⁸ and some of them even by water⁹ into their component amine and aldehyde. It is important, therefore, to bear in mind this fact whenever reduction is carried out in acid media, for

¹O. Anselmino, Ber. 41, 621 (1908).

²Zechmeister and Trucka, Ber., 63B, 2883 (1930).

³E. C. Wagner et al., J. Am. Chem. Soc., 54, 660, 3698 (1932); 55, 724 (1933).

⁴Miller and Plochl, Ber., 25, 2020-2071 (1892).

⁵Wagner et al., op. cit.

⁶J. S. Buck, J. Am. Chem. Soc., 53, 2194 (1931).

⁷Anselmino, op. cit.

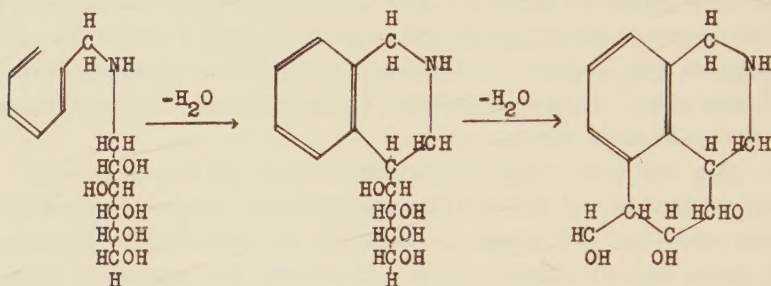
⁸A. Maihle, Bull. Soc. Chim., 25, 321 (1913); 27, 229 (1920); 35, 379 (1924).

⁹Langman, Healy, and Dut, J. Indian Chem. Soc., 4, 75 (1927).

under such conditions one has to contend with two different reactions, hydrolysis and reduction, and, unless the velocity of the latter is relatively much higher than that of the hydrolysis, very little of the desired secondary amine would be formed.¹⁰

Catalytic hydrogenation is undoubtedly the most general and useful of the methods of reduction of the Schiff's bases. In this case hydrogenation in the presence of platinum oxide was employed for the reduction of benzalglucamine to the secondary amine. The Schiff's base is formed very readily by interaction of benzaldehyde with glucamine.¹¹

The purpose of the autocondensation of benzylglucamine was the possible formation of a substituted iso-quinoline type compound by the loss of water. This product could then perhaps lose a second molecule of water and give rise to a three ring heterocyclic compound:



Since upon treatment of benzylglucamine with hydrogen chloride and bromide only the corresponding amine hydrohalides were obtained, the more drastic treatment with liquid anhydrous hydrogen fluoride was attempted in order to bring about the autocondensation. The results obtained are inconclusive since it was not possible to isolate and identify any condensation product aside from some benzylglucamine hydrofluoride. The condensation mixture consisted of a yellowish-brown, non-volatile, non-crystallizable, readily charring, syrupy material which was miscible with water. Similar syrupy products were obtained when concentrated sulfuric acid was used as the condensing agent.

¹⁰Wagner et al., op. cit.

¹¹L. Maquenne et E. Roux, Compt. rend., 132, 980 (1901).

Experimental

Glucamine.--The glucamine¹² used was obtained in a very crude form (appx. 25%), from the E. I. du Pont de Nemours Company of Wilmington, Delaware, where it was prepared by simultaneous condensation-reduction of glucose and ammonia under high pressure (1500 lbs) of hydrogen at a temperature of 110° to 120° C. in the presence of finely divided nickel catalyst.¹³ Purification was necessary before use, and this proved to be quite a difficult process because of the hygroscopic character of the glucamine. Decolorization with animal charcoal in boiling absolute ethyl alcohol was resorted to in order to obtain a fairly pure glucamine; later the Schiff's base itself was used for the removal of glucamine from the crude product.

Preparation of Benzal Glucamine.--¹⁴Ten grams of glucamine, ten grams of benzaldehyde and 100 cc. of absolute ethyl alcohol were refluxed for one hour on the steam bath. On cooling and scratching, a voluminous crystalline precipitate came down. Eight grams were obtained, melting at 161°-163° C. Benzal glucamine crystallizes from ethyl alcohol in very small, fiber-like needles, which are anisotropic and show oblique extinction at an angle of 20° to 35°. In the same manner anisal glucamine was also prepared. It is also formed as crystalline needles melting at 159°-160° C.

Preparation of Benzylglucamine.--The reduction of benzal-glucamine was carried out in a simple hydrogenation apparatus under a hydrogen pressure of 60 to 70 cm. of mercury and in the presence of active platinum oxide catalyst prepared from chloroplatinic acid.¹⁵ Two grams of benzalglucamine dissolved in 120 cc. of absolute methyl alcohol were placed in the hydrogenation flask into which 0.2 grams of the catalyst had already been added. The air was swept repeatedly from the system with a stream of hydrogen gas. The necessary hydrogen pressure was then attained by forcing the mercury from the manometer into a raised reservoir and shaking of

¹²Ling and Nanji, J. Chem. Soc., 121, 1682 (1922); Maquenne et Roux, op. cit.

¹³R. Flint and P. Salzberg, U. S. Patent 2016962-3.

¹⁴Maquenne et Roux, op. cit., 981.

¹⁵R. Adams et al., J. Am. Chem. Soc., 44, 1399 (1922); 49, 1099 (1927), etc.

the reaction flask commenced. Absorption of hydrogen was very rapid and the reduction was completed in less than an hour. The alcoholic solution was filtered and upon removal of most of the alcohol, benzylglucamine crystallized out, of which 1.8 grams were obtained, melting at 141-142°C. Both the amine hydrochloride and hydrobromide came down in crystalline form as irridescent plates upon passing the gaseous acid through the alcoholic solution of the amine. The hydrochloride melted at 194°-195°C., and the hydrobromide at 190°-191° C. The benzylglucamine hydrofluoride was formed in crystalline prismatic needles which showed parallel extinction and melted at 188°C.

The hydrogen fluoride was obtained in anhydrous condition compressed in a special tank from the E. I. du Pont de Nemours Company. When required for use, the gaseous acid was led through a copper spiral in which it was liquefied by cooling the spiral condenser with an ice-salt bath. The liquid hydrogen fluoride was collected in platinum or copper vessels into which the reactants were added. Upon completion of the reaction, the hydrogen fluoride was allowed to evaporate, and the residue after neutralization was worked up in any manner deemed advisable for the particular case involved.

The autocondensation of benzylglucamine was carried out both in open platinum vessels and in closed iron bomb tubes. In the former case the benzylglucamine was added to the hydrogen fluoride in a platinum crucible and the reaction mixture allowed to stand overnight or longer if necessary. The reaction mixture was then extracted with alcohol and the traces of hydrofluoric acid neutralized with an alcoholic solution of sodium hydroxide. The alcohol was then removed under vacuo and the syrupy residue treated in many ways in order to isolate and identify a condensation product. The reaction mixture from the iron bomb tubes was treated in the same manner. Some of the iron bomb tubes were heated at 50° and at 100° C. for several hours in addition to standing at room temperature for one day or more. In both cases the resulting syrups could not be analyzed nor identified.

Conclusion and Summary

It is not possible to bring about an autocondensation of benzylglucamine by means of a strong dehydrating agent so that

isoquinoline type compounds are formed.

Benzylglucamine was prepared by the catalytic reduction of benzalglucamine with hydrogen in the presence of platinum oxide.

CONDENSATION OF SOME CYCLIC KETONES
BY MEANS OF THE HALOGEN ACIDS

It is well known that the presence even of small amounts of mineral acids brings about autocondensation of both cyclopentanone and cyclohexanone. Explicit instructions¹⁶ are given in the preparation of these ketones for the complete removal of all traces of acids to insure their stability. The autocondensation of cyclopentanone and cyclohexanone by means of sulfuric acid and by sodium ethylate have been studied by several investigators.¹⁷ The products obtained in these autocondensations are ketonic dimers and trimers, and cyclization of the trimer to an aromatic nucleus.

It was possible to induce the autocondensation of these ketones by means of anhydrous gaseous and liquid hydrogen fluoride, chloride, and bromide, and to obtain the same products as those with the stronger condensing agents with but one exception: no triphenylene was obtained from cyclohexanone.

The amounts of the various products obtained depended upon several factors, primarily upon the length of treatment and the temperature and to some extent upon the halogen acid used. The order of effectiveness of the halogen acids in bringing about the autocondensation is: hydrofluoric, hydrochloric, hydrobromic; but, since the difference is not very great, a quantitative study was not possible. There is but a slight difference in the relative ease and extent of the autocondensation of cyclopentanone and cyclohexanone under comparable conditions, the tendency of the latter being slightly more pronounced.

In general, the longer the treatment, or the higher the temperature of condensation, the smaller the amount of the dimer and the larger the amount of the trimer and resinous polymeric

¹⁶Baeyer, Ann., 278, 101 (1894).

¹⁷O. Wallach, Ber., 29, 2955 (1896); 30, 1094 (1897).
N. Zelinski and N. Shuikin, J. Russ. Phys. Chem. Soc., 62, 1343 (1930); C.A., 25, 2520 (1931).
B. Samdahl and B. Hansen, J. Pharm. Chim., 19, 573 (1934).
M. Kaufman, Ber., 41, 3726 (1908).

substances produced, Bomb tube reactions with the liquid halogen acids were more effective than open tube reactions with the gaseous acids. The use of a very large excess of the halogen acid had no appreciable effect on the extent of the condensation. In all cases when the treatment exceeded four hours at room temperature all the original ketone disappeared; the differences observed, therefore, deal only with the extent of the autocondensations.

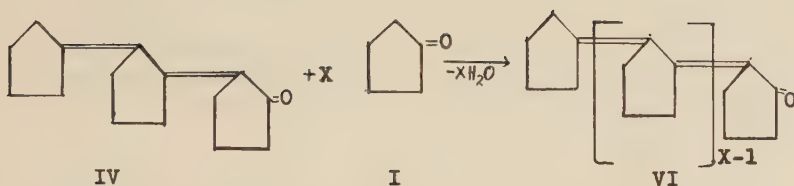
Table 1, composite of a great number of experiments, summarizes the effects of the various factors.

TABLE 1

Expmt.	Ketone	Acid	Conditions			Products				
			Ves-sel	Time	Temp	Rec. Ke-tone	Dimer	Trimer	Resins	Hydro-carbon
14	8 gms. cyclo-hexan-one	3.5g. HCl	Bomb tube	36 days	Room		3.0g.	1.2g.	3.4 g.	
18	8 gms. cyclo-hexan-one	8.5g. HBr	Bomb tube	36 days	Room		3.1g.	1.2g.	3.4 g.	
23	8 gms. cyclo-hexan-one	6 g. HCl	Bomb tube	7 hrs.	50-60		0.5	3.5	3.5	
27	8 gms. cyclo-hexan-one	Sat. HCl	Open tube	12 hrs.	Room		6.7		0.3	
39	40 gms, cyclo-pentanone	20 g. HCl	Bomb tube	15 days	Room	<u>6</u> ?	5.2	4.5	13.5	5 g.
40	15 gms. cyclo-pentanone	10 g. HF	Open tube	12 hrs.	Room	3.9	1.2	5.0	4.0	?

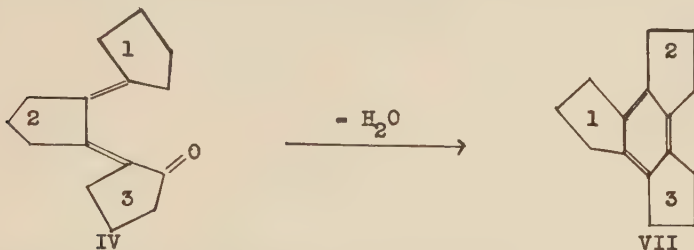
The course of the autocondensation reaction is undoubtedly the same for both cyclopentanone and cyclohexanone. Schematically it can be represented as follows:

4.



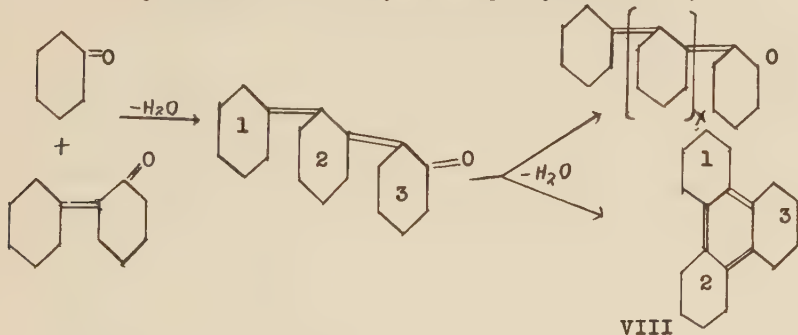
The trimer may also condense intramolecularly with the α -carbon atom of the first cyclopentylidene nucleus to give rise to the aromatic nucleus VII, tricyclotrimethylenbenzene:²⁰

5.



The corresponding product from the autocondensation of cyclohexanone is the hydrocarbon dodecahydro-triphenylene, VIII;²¹

6.

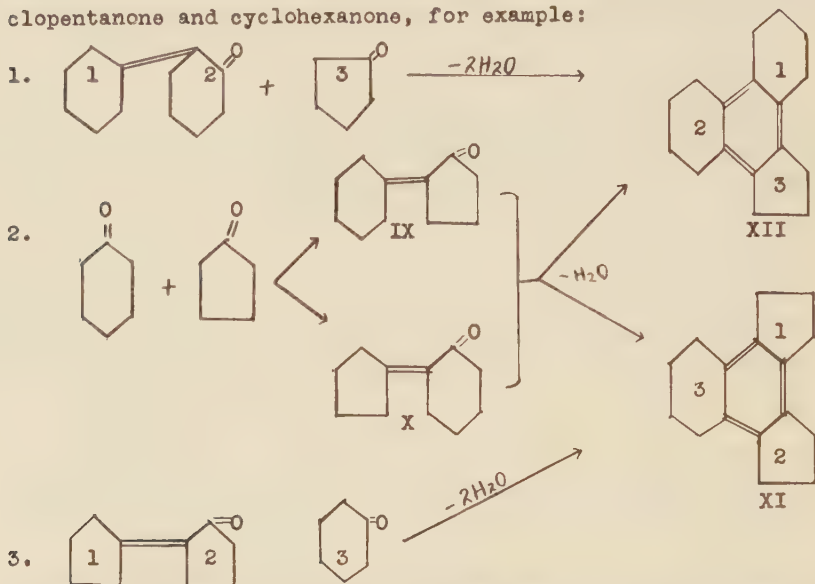


No dodecahydro-triphenylene was obtained from the condensation products of cyclohexanone with the halogen acids. The reason for this is probably that, if formed, the yield is quite small as in the case of cyclopentanone, but since its formation is accompanied with that of the polymeric resins it is impossible to separate it from them; for, while the melting point of the tricyclotrimethylenbenzene is low (m.p. 96° C) and the substance readily distills

²⁰Ibid., 30, 1096 (1897). ²¹Mannich, Ber., 40, 154 (1907).

in vacuo, that of the dodecahydro-triphenylene is high²² (m.p. 232° C) and can not be isolated by vacuum fractionation.

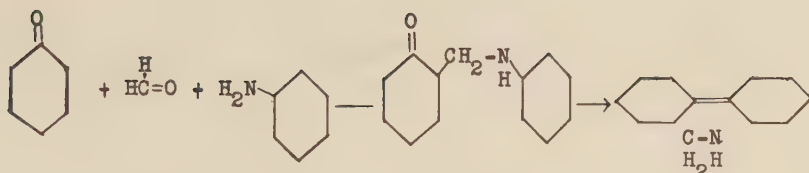
Several attempts were made to prepare the analogous mixed substituted aromatic hydrocarbons by the intercondensation of cyclopentanone and cyclohexanone, for example:



Neither of these two possible hydrocarbons, XI and XII, was isolated in any of the three cases. The resulting products were very complicated mixtures of 2-cyclopentylidenecyclopentanone, 2-cyclohexylidenecyclohexanone, possibly also 2-cyclopentylidenecyclohexanone, 2-cyclohexylidenecyclopentanone (X and IX respectively), plus complicated trimers, and, worst of all, high molecular polymeric resins. These mixtures defied analysis by fractionation, for even narrow range boiling fractions were shown to be mixtures of two or more components by the fact that mixtures of crystalline 2,4-dinitrophenylhydrazones were formed. A further complication is encountered in that each of the hydrazones can exist in two stereoisomeric forms (see page 14).

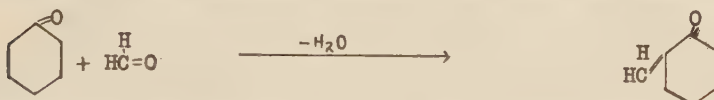
The condensation of cyclohexanone with formaldehyde and cyclohexylamine by means of the halogen acids was also studied. This attempt had in view the separation of a heterocyclic combination analogous to those of the hydrocarbons:

²²Ibid.



But considering the complicated condensation that takes place readily between formaldehyde and cyclohexanone under these conditions, it is not surprising that this compound was not obtained.

The interaction of cyclopentanone or cyclohexanone with formaldehyde should, by analogy, yield as the first condensation product a 2-methylenecycloketone. The reaction, however, in the



presence of the halogen acids is very rapid and exothermic resulting in the formation of high molecular weight resins in yields as high as 70 to 80%. Aside from the resins, only small quantities of the ketonic dimers could be isolated.

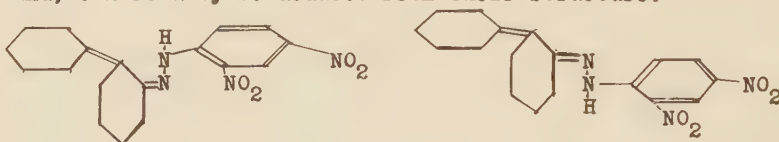
The various resins obtained both from the autocondensations of cyclopentanone and cyclohexanone and their condensations with formaldehyde were made the object of further study in order to throw some light upon their chemical nature. On vacuum fractionation at 15 mm. pressure they began to distil at about 230° C. as amber colored viscous liquids. The boiling point rose gradually without a break up to about 320° C. On cooling the various fractions became semisolid, non-crystalline resins, very soluble in benzene and acetone from which they could be precipitated in solid form by addition of alcohol. In the solid form the resins from the autocondensations softened at 80°-100° C., those from the condensations with formaldehyde at 160° C. and above. Molecular weights determined by the lowering of the freezing point of benzene ranged from six hundred for the lower boiling resins to nine hundred for the higher boiling, and above a thousand for the residues. No derivatives could be prepared with any of the common ketonic reagents, but these can hardly be expected from such complicated structures as these compounds may have.

In order to determine the effect of α substituents on the autocondensation of cyclic ketones by means of halogen acids, the

autocondensations of 2-ethylcyclohexanone and 2-methyl-4-isopropylcyclohexanone, menthone, were also investigated.

Neither of these two compounds, even upon so drastic a treatment as heating in a bomb tube at 100 C. for eight hours, underwent autocondensation. In both cases a slight coloration developed, but the initial material was recovered practically in its entirety in every experiment. It was then identified by its boiling point, refractive index, and the melting point of its 2,4-dinitrophenylhydrazone. In the case of menthone, there was a change in the optical rotation only, which dropped from $(\alpha)_D -4^\circ$ to 0° . But this is to be expected since 1-menthone, $(\alpha)_D -27^\circ$, racemizes readily even with traces of hydrochloric or other mineral acids.²³

The reagent 2,4-dinitrophenylhydrazine was used extensively in this phase of the work to prepare derivatives for identification of the ketones used and produced.²⁴ In the course of this work it was observed that although the 2,4-dinitrophenylhydrazone of 2-cyclohexylidenecyclohexanone is an orange-colored crystalline substance, prismatic needles melting at 151° C, at times there was also obtained another form, yellow crystalline leaflets melting at 131° C. Both forms of the 2,4-dinitrophenylhydrazone contain the same percentage of nitrogen which corresponds to that calculated for this compound. The obvious conclusion, in view of these facts, is that these compounds are two stereoisomeric forms of the hydrazone, and, can readily be deduced from their structure:²⁵



Further study of the conditions of the formation of these two stereoisomeric hydrazones, revealed that the rarer, low-melting isomer was formed only in acid solutions, while the high-melting isomer was obtained in both acid and neutral solutions. It was then observed that while it was not possible to change the low-melting, yellow isomer to the higher-melting, orange one by any of

²³Beckman, Ann., **250**, 334 (1889); Ber., **42**, 846 (1909).

²⁴C. Allen, J. Am. Chem. Soc., **52**, 2955 (1930).

²⁵Armand, Kon, and Nutland, J. Chem. Soc., 3106 (1926).
Vavon et Apchie, Bull. soc. chim., **43**, 669 (1928).

several different treatments attempted, the reverse could be accomplished, merely by recrystallizing the higher-melting isomer from alcohol through which dry hydrogen chloride gas had been bubbled for a short time. The resulting product contained two distinct crystalline forms, more than 60% of which was the lower-melting isomer. By further recrystallization the two forms can easily be separated completely. It is interesting to note that this conversion is contrary to that expected for usually it is the less stable, lower-melting, isomer that is converted to the more stable, higher-melting form.

Experimental

Preparation of Cyclopentanone and Cyclohexanone.--Cyclopentanone was prepared by the dry distillation of adipic acid (200 gms.) with barium oxide (10 gms.) from a lead bath (280°-290° C.).²⁶ The product was then fractionated and the fraction boiling at 129°-130° C. was retained. Its 2,4-dinitrophenylhydrazone forms readily in crystalline, orange, prismatic needles melting²⁷ sharply at 145° C. The cyclohexanone used was prepared by the oxidation of technical cyclohexanol with potassium dichromate in sulfuric acid by the method of V. Baeyer²⁸ and also by the improved method of Osterberg and Kendall.²⁹ The fraction that distilled over at 155°-156° C. was retained. Its 2,4-dinitrophenylhydrazone forms readily in bright yellow crystalline flakes, melting³⁰ at 156.5°-157° C.

Preparation of 2-ethylcyclohexanone.--2-ethylcyclohexanone was prepared by the condensation of 2-chlorocyclohexanone with ethylmagnesium bromide.³¹ The 2-chlorocyclohexanone was prepared by direct chlorination of cyclohexanone³² with chlorine gas in the presence of calcium carbonate, which removes the hydrochloric acid

²⁶Vavon et Apcbie, op. cit., 667.

²⁷Allen, op. cit., 2958.

²⁸Ann., 278, 101 (1894).

²⁹J. Am. Chem. Soc., 42, 2616 (1920).

³⁰Allen, op. cit.

³¹G. Lissier, Compt. rend., 141, 1033 (1905).

³²Kotz und Grethe, J. Prakt. Chem. (2) 80, 487 (1909).
Bouveault et Chereau, Compt. rend., 142, 1087 (1906).

formed by the chlorination. (The presence of hydrochloric acid brings about autocondensation of the chlorocyclohexanone as well as of the cyclohexanone.) Chlorine gas was passed through a mixture of 50 gms. of cyclohexanone, 30 gms. of calcium carbonate and 40 cc. of water at a temperature of 25°-28° C. till no more carbon dioxide was being given off. The mixture was then extracted with ether, the ether layer washed and dried with anhydrous sodium sulfate, and after removal of the ether, the residue was fractionally distilled in vacuo. There was obtained 35 gms. of the 2-chlorocyclohexanone boiling at 105°-110° C. at 25-30 mm. and melting at 22° C. It formed two stereoisomeric 2,4-dinitrophenylhydrazones, an orange crystalline form melting at 115° C. and a red form melting with decomposition at 193° C. The ethylmagnesium bromide was prepared in the usual manner from 7 gms. of magnesium turnings and 27 gms. of ethylbromide in 50 to 60 cc. of anhydrous ether. To the ethylmagnesium bromide 33 gms. of the 2-chlorocyclohexanone were added dropwise with cooling and stirring. The reaction mixture was then treated with water, extracted with ether, the ether layer washed and dried, and upon removal of the ether the residue was fractionated in vacuo. There was obtained 25 gms. of 2-ethylcyclohexanone boiling at 104° C. at 25 mm. Its 2,4-dinitrophenylhydrazone melted at 141°-142° C.

Preparation of 2,4-dinitrophenylhydrazones.--³³The hydrazones were prepared by treating a methyl alcoholic solution of the ketone in the cold with a slight excess of the hydrazine stock solution. The hydrazine stock solution was prepared as follows: 2 grms. of the 2,4-dinitrophenylhydrazine were dissolved in 5 cc. of concentrated sulfuric acid by warming on the steam bath if necessary. The clear solution is then cooled and added to 45 cc. of absolute methyl alcohol. This solution will keep for over a month unless crystallization of the hydrazine sulfate sets in.

The cyclohexylamine used was obtained from the Monsanto Chemical Company of St. Louis, Missouri. The fraction used boiled at 134°-135° C. at 750 mm., the hydrochloride of which melted at 205° C.

The 1-menthone was prepared by Dr. A. Bloodgood, but was racemized to the extent of $(\alpha)_D -4^\circ$ from $(\alpha)_D -27^\circ$. It boiled at 89.5°- 90.5° C. at 25 mm. It readily formed a crystalline 2,4-

³³Allen, op. cit. Ferrante and Bloom, Am. J. Pharm., 105, 381 (1933).

dinitrophenylhydrazones, orange prismatic needles melting at 144.5°C .³⁴

The formaldehyde used was in the form of trioxymethylene.

The hydrogen chloride was obtained by dehydration of a solution of hydrochloric acid with concentrated sulfuric acid in a simple drop-funnel gas generator.

The hydrogen bromide was generated by the reaction of bromine on boiling tetraline in an all-glass apparatus. The hydrogen bromide was scrubbed before use through a short tower of calcium chloride and then through a similar one of naphthalene to remove traces of bromine. Both acids were liquefied when necessary by cooling the reaction vessel with an acetone- CO_2 bath through which dry air was bubbled vigorously (temp. -110°C .).

The condensations.--The reactants were weighed in the bomb tube, the tube placed in the cooling bath, and the hydrogen halide collected by liquefaction. When the required amount of the acid had been collected, the bomb tube was sealed off by drawing out one end to a fine strong capillary while still in the cooling bath. It was then placed in a steel jacket and allowed to come to room temperature or heated to a higher temperature as required. Before opening, the bomb tube was cooled again to the same temperature at which it was sealed; it was then opened by breaking the tip of the capillary with a pair of pliers. The excess acid was then allowed to escape and all traces removed by suction of the water pump. The reaction mixture was then extracted with ether or acetone and fractionated under vacuo. Open tube condensations were carried out by saturating the reactants at room temperature with the gaseous acid and then allowing to stand at room temperature for one or more days or warming at 50°C . for several hours. The reaction mixture was analysed in the same manner as that of the bomb tube reaction.

Conclusion

Cyclic ketones undergo autocondensation in the presence of hydrogen fluoride, chloride, and bromide as long as both α -carbons are unsubstituted. The main product of the autocondensation is a dimeric ketone but trimers and polymers as well as an aromatic nucleus are also formed.

³⁴Allen, op. cit.

Summary

The condensation of cyclopentanone and cyclohexanone with hydrogen halides has been studied and several products obtained.

Cyclic ketones having a methyl or an ethyl group on either of the α -carbons do not undergo autocondensation.

Condensations of cyclohexanone and cyclopentanone with formaldehyde yield a high percentage of a high-melting resin.

Some of the 2,4-dinitrophenylhydrazone of the ketonic products were prepared in two stereoisomeric forms. The syn-anti-transformation of one of these was studied.

Intercondensations between cyclopentanone and cyclohexanone were attempted.

CONDENSATIONS OF AROMATIC NUCLEI
WITH FORMALDEHYDE

Formaldehyde has been used extensively in many types of organic condensations.³⁵ It undergoes aldol-like condensations with aldehydes and ketones³⁶ and with many organic acids,³⁷ the products being many and varied depending upon the reagents and conditions.

Interesting condensation products are obtained by the interaction of formaldehyde with aromatic compounds; for example, with benzene, diphenylmethane is formed; with mesitylene, hexamethyldiphenylmethane;³⁸ and analogous diaryl substituted methanes with toluene³⁹ and naphthalene.⁴⁰ In practically all of these condensations concentrated sulfuric acid or a metal halide is used as the condensing agent. The yields are usually quite low.

Aromatic compounds condense in a somewhat different manner with formaldehyde when zinc chloride and hydrochloric acid are used as the condensing agents. By this type of condensation G. Blanc⁴¹ was able to prepare in good yields a series of chlormethylene aromatic hydrocarbons, as for example, benzyl chloride from benzene and trioxymethylene. This reaction has proved so successful and so readily adaptable for other similar preparations that it has been made the object of extended study by other investigators,⁴²

³⁵J. E. Orloff, "Formaldehyd," J. A. Barth, Leipzig, 1927, pp. 61-110 and 243-264.

³⁶Koch and Zerner, Monatsh., 22, 443 (1902).
B. Tollens, P. Wigand, Ann. 265, 316 (1891).
M. Apel und B. Tollens, Ber., 27, 1087 (1894).

³⁷Howard and Perkin, Proc. chem. soc., 189, 46 (1897).
Bottomley and Perkin, J. Chem. Soc., 73, 330 (1898); 77, 294 (1900).

³⁸A. Baeyer, Ber., 5, 1097-8 (1872); 6, 220 (1873).

³⁹J. Weiler, Ber., 7, 1181 (1874).

⁴⁰J. Grabowski, Ber., 7, 1605 (1874).

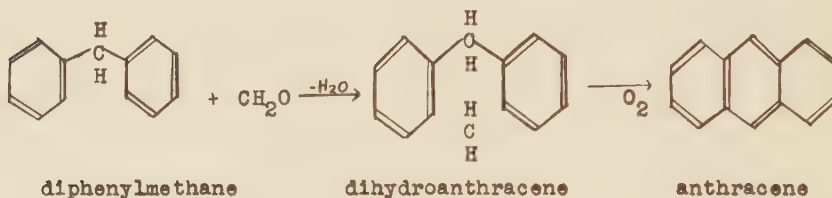
⁴¹G. Blanc, Bull. soc. chim., 33, 313 (1923).

⁴²R. Quelet et al., Compt. rend., 195, 155 (1932); 198,

particularly R. Quelet who used stannic and aluminum chlorides as well as zinc chloride in conjunction with hydrochloric acid.

No condensations of aromatic or substituted aromatic hydrocarbons and formaldehyde by means of the halogen acids alone are reported. The condensations attempted, therefore, were studied in order to determine whether condensation took place, and, if so, whether it occurred in the manner of the Blanc reaction or by the formation of diarylmethanes.

Diphenylmethane, which may be considered as a condensation product of benzene and formaldehyde, was chosen as one of the reactants because of the possibility of its condensing with a molecule of formaldehyde on the *ortho-ortho* prime position to give rise to dihydroanthracene which then can be further oxidized to anthracene:



Condensations of diphenylmethane with trioxymethylene were attempted with liquid anhydrous hydrogen chloride and bromide. The reaction in bomb tubes was attempted both at room temperature for several days and at 100° C. for ten hours. Practically all of the diphenylmethane used in these experiments was recovered; no dihydroanthracene nor anthracene was detected even in traces. There was formed only a very small amount of a high-boiling, brownish, resinous oil, which could not be purified for further analysis.

Nitrobenzene and nitrophenols have been condensed with formaldehyde⁴³ by means of concentrated sulfuric acid. The products obtained in these condensations were the various possible disubstituted diphenylmethanes⁴⁴ in small amounts. The condensation of

102 and 2256 (1934); Bull. soc. chim., (4)53, 851 (1933); (5)2, 684 (1935), 3, 1794 (1936).

⁴³M. Schopff, Ber., 27, 2321 (1894).

⁴⁴F. Ullmann und E. Naef, Ber., 33, 905 (1900).
H. Bucherer und F. Seyde, Ber., 40, 859 (1907).
D. R. P. 58944; 59003; 84379; 179020, etc.

nitrobenzene with formaldehyde by means of hydrochloric acid, however, may yield nitro substituted benzylchlorides in the manner of Blanc's reaction as well as dinitrodiphenylmethanes.

The condensations of nitrobenzene with trioxymethylene were attempted in bomb tubes at room temperature, at 50° C. and at 100° C. Both hydrogen chloride and bromide in the liquid state were used. In no case was there any condensation product obtained in significant amounts. In every case the nitrobenzene used was recovered practically quantitatively.

The ease with which nitrophenols, phenols, and aniline condense with formaldehyde, in the presence of strong condensing agents, seems to indicate a direct relationship between the electronic character of the substituent group and the extent of the formaldehyde condensation. Thus, while phenols and aniline (OH and NH₂, activating groups) condense readily with formaldehyde,⁴⁵ nitrobenzene and benzoic acid (NO₂ and COOH, deactivating groups) do so with difficulty.

Benzene, from this point of view, lies intermediately between these two extreme groups. But attempted condensations with trioxymethylene in the presence of anhydrous liquid hydrogen chloride and bromide yields no diphenylmethane and only a trace of benzyl halide.

The condensation of aromatic amines with aldehydes has been the subject of numerous investigations. It is beyond the scope of this work to undertake a detailed discussion of these various condensations. Briefly, there are three possible ways in which an amine may condense with an aldehyde:

First: a Schiff's base may be formed.⁴⁶ This is the most common condensation of amines with aldehydes and proceeds without condensing agents.

Second: the Schiff's base may absorb a second molecule of the amine to form a dimer.⁴⁷ This is usually the product of the

⁴⁵M. Schopff, op. cit.

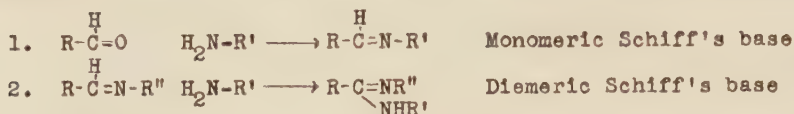
⁴⁶H. Schiff, Ann., 131, 118 (1864); 140, 92 (1866); 148, 330 (1868); 201, 355 (1880).

A. Eibner, Ann., 328, 121 (1903).

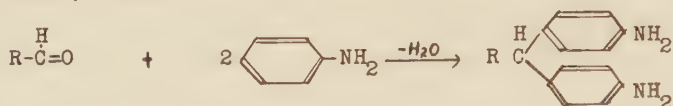
Ingold et al., J. Chem. Soc., 121, 2381, 2793 (1922); 123, 2745 (1923).

⁴⁷v. Miller und Plochl, Ber., 25, 2020 (1892); 27, 1281 (1894); 29, 1462 (1896).

simple condensation with alkylaldehydes, but even arylaldehydes will absorb two molecules of the amine when a condensing agent is present.⁴⁸



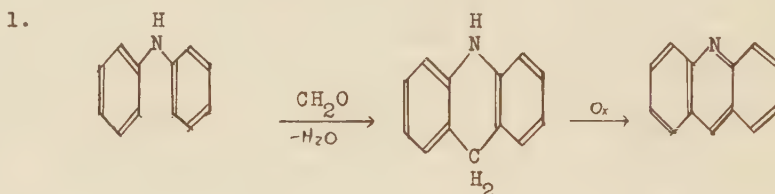
Third: the condensation may take place through the para-hydrogen of the arylamine giving rise to amino substituted di- or tri-aryl methanes,⁴⁹ thus:



This type of condensation takes place only in the presence of strong condensing agents. With aromatic aldehydes and properly substituted aromatic amines leucobases of the triphenylmethane series can be prepared by means of dehydrating condensing agents.⁵⁰

The condensation of secondary aromatic amines with aldehydes has not been studied extensively. This is particularly true of their condensations with formaldehyde. There is but one reported condensation of a triarylamine with an aldehyde.⁵¹

The condensation of diphenylamine with formaldehyde may proceed in either or both of two ways:



⁴⁸Mazzara, Gazz. chim. Ital., **15**, 44 (1885).

⁴⁹Mazzara, Ber., **18**, 334 (1885).

O. Tschachev, Ber., **19** 2463 (1886); **21**, 188 (1888).

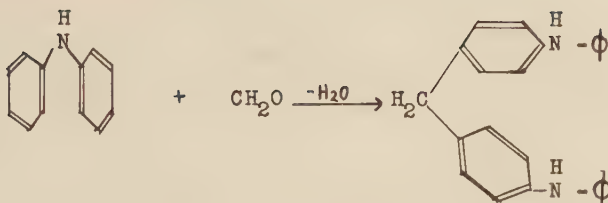
F. Stotz, Ber., **20**, 615 (1887).

R. Aschutz, Ber., **17**, 1078 (1884).

⁵⁰O. Fischer, Ann., **206**, 83 (1880). Also ref. 45, 46, 47.

⁵¹Haeussermann, Ber., **39**, 2764 (1906).

2.



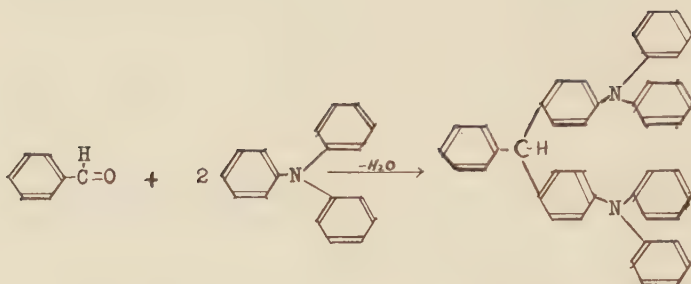
In the first case 8,10-dihydroacridine results which may be oxidized to acridine,⁵² while in the second case a di(phenylamino) substituted diphenylmethane is formed.

Condensations attempted with solid diphenylamine, trioxymethylene, and liquid hydrogen chloride and bromide in bomb tubes yielded only the diphenylaminehydrohalides. There was no condensation between the amine and the aldehyde probably because of the lack of intimate contact, for reactions carried out in aqueous solutions of hydrochloric and hydrobromic acids brought almost complete condensation. The product, a greenish colored substance, was insoluble in most solvents, did not melt even at 360 C., and contained 7.2% of nitrogen. As no acridine nor dihydroacridine was obtained, it was concluded on the basis of the percentage nitrogen alone that this compound is 4,4'-di(phenyl-amino-)diphenylmethane. Because of the insolubility of this compound in most solvents employed it was not possible to determine its molecular weight; and since its fusion point is very high, it is not possible to burn it completely by the micro-Dumas method. The nitrogen content determined in this manner is very low for such a compound. The value reported was obtained by the micro-Kjeldahl method.

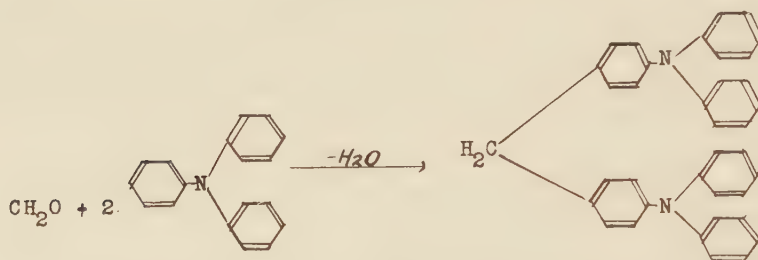
The condensation of triphenylamine with benzaldehyde was studied by Haeussermann⁵³ in 1906, with concentrated sulfuric acid as the condensing agent. The product was a green, insoluble, high-fusing compound, which was considered as the 4,4-di(phenylamino-) triphenylmethane: this conclusion was reached on its nitrogen content alone which was found to be 4.4% by the Kjeldahl method as compared with 4.8% calculated for the compound.

⁵²O. Fischer, *Ber.*, 28, 1335 (1895).
C. Graebe und H. Caro, *Ann.*, 158, 279 (1871).

⁵³Haeussermann, *op. cit.*,



Were the analogous condensation with formaldehyde to follow the same course, the corresponding 4,4-di(phenylamino-)diphenylmethane should be formed:



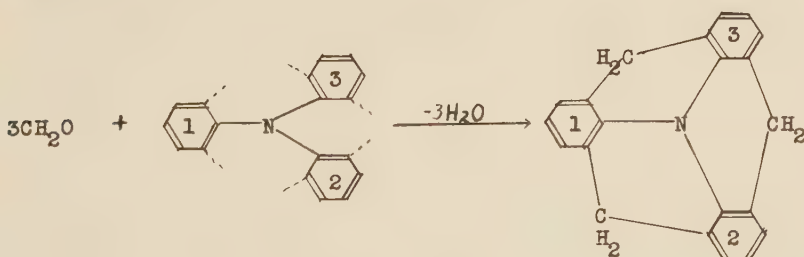
The condensation of triphenylamine with aqueous formaldehyde in the presence of either hydrochloric or hydrobromic acid on the water bath proceeds to completion in less than three hours. The compound formed is a light green, insoluble, high-fusing substance, very much like that described by Haeussermann for the benzaldehyde condensation. On the basis of analogy alone it may be concluded that this compound is the para substituted diphenylmethane; but this is ruled out by the following two considerations: first, the compound obtained contained 4.8% nitrogen while the calculated for the diphenylmethane type is 5.6%; and second, it was observed that a minimum of three moles of formaldehyde for every mole of triphenylamine were necessary for complete condensation of all of the triphenylamine, instead of one-half mole of formaldehyde per mole of triphenylamine as required by the Haeussermann type condensation. Whenever less than three moles of formaldehyde per mole of triphenylamine were used, only one-third mole-ratio of the amine combined and the excess could be recovered quantitatively. Table 2 illustrates this point. Any proposed structure for this compound,

TABLE 2

	$\phi_3\text{N}$	CH_2O 38%	Mole ratio $\text{CH}_2\text{O}/\phi_3\text{N}$	Conden- sation Product	Recovered $\phi_3\text{N}$	Combining ratio $\text{CH}_2\text{O}/\phi_3\text{N}$
1.	0.5 gms.	1.5cc.	3 : 1	0.45gms.	0.05	appx. 3 : 1
2.	0.5 gms.	1.0cc.	2 : 1	0.28gms.	0.20	3 : 1
3.	0.5 gms.	0.5cc.	1 : 1	0.14gms.	0.35	3 : 1
4.	0.5 gms.	0.0	0 : 1	0.00gms.	0.50	
5.	1.5 gms.	10 cc.	7 : 1	1.7 gms.	0.0	3 : 1

therefore, must bear out this fact as well as satisfy the nitrogen content requirements.

All condensations of the third type between aromatic amines and aldehydes⁵⁴ have been shown to yield para substituted di- or tri-phenylmethanes. There is no reason, however, to presume that no ortho substitution can take place. In the case of aromatic amines the ortho position is also greatly activated, and condensation should take place almost as readily through the ortho as the para hydrogen. This in fact takes place in the formation of acridine and N-substituted acridines by condensation of diphenylamine with chloroform,⁵⁵ formic and oxalic acids,⁵⁶ and acetic acid⁵⁷ by means of zinc chloride or aluminum chloride. In the same manner then three molecules of formaldehyde combining with the six ortho positions in one molecule of triphenylamine should produce the compound shown:



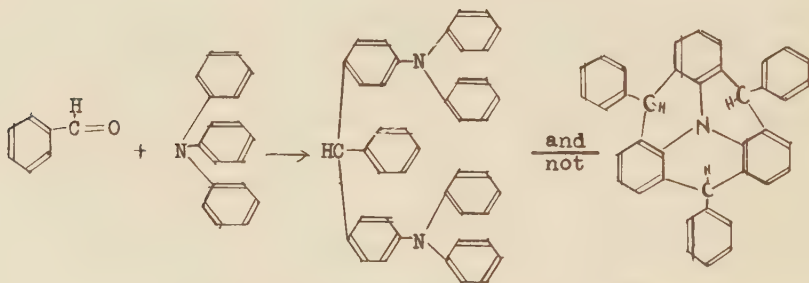
⁵⁴See p. 22. ⁵⁵F. Koerner, Ber., 17, 102 (1887).

⁵⁶A. Bernthsen, Ann., 224, 10 (1884).

⁵⁷Fischer und Rudolf, Ber., 15, 1505 (1885).
Blum, Ber., 62, 884 (1929).

The nitrogen content calculated for this compound is 5.0% which is close to that found (4.8%). The structure also accounts for the observed condensation ratio of three moles of formaldehyde for each mole of triphenylamine. It should be noted again that these two considerations are the only basis for the proposed structure, for, neither carbon-hydrogen analyses nor molecular weight determinations could be carried out. Furthermore, no simple derivatives could be prepared; it was possible to nitrate it by means of concentrated nitric acid, but oxidation accompanied this reaction. The nitrated product obtained was not crystalline and contained 14.1% nitrogen which can be accounted for by the tri-nitro compound (13.4% N).

The condensation of triphenylamine with benzaldehyde was carried out by means of aqueous hydrochloric acid in order to determine whether the compound of Haeussermann⁵⁸ or an analog of the triphenylamine-formaldehyde condensation product is formed. The condensation took place readily, with complete removal of the triphenylamine even when less than a mole of benzaldehyde per mole of triphenylamine was used. The nitrogen content of this condensation product was 4.9% (microKjeldahl) which is in agreement with the compound of Haeussermann.



Experimental

The nitrobenzene used was a commercial high-grade product. It was further purified before use by vacuum distillation. The fraction used boiled at $88^{\circ}\text{--}90^{\circ}\text{C}$. at 12 to 15 mm. and melted at 5.6°C .

The diphenylmethane was a student preparation. It was fractionated in vacuo and then further purified by crystallization.

⁵⁸Haeussermann, op. cit.

The fraction used boiled at $130^{\circ}\text{--}1^{\circ}\text{ C.}$ at 15 mm. and melted at 24° C.

The benzene was Merck's thiophene free, chemically pure grade.

The condensations were carried out in pyrex bomb tubes in the manner described under the condensation of the cyclic ketones, p. 17.

The diphenylamine used was of unknown origin, bluish gray, and crystalline. When recrystallized it melted at 53° C. It formed a hydrochloride melting at 230° C. with decomposition. On standing exposed to air the hydrochloride became intense blue in color.

Preparation of 4,4'-di(phenylamino-)diphenylmethane.--Six grs. of diphenylamine, 4 cc. of 38% formaldehyde, and 10 cc. of conc. hydrochloric acid were refluxed for two hours on the steam bath. The resulting dark green substance was collected on a filter and washed thoroughly with water; when dried it weighed 6 grs. but did not melt even at 360° C. Steam distillation both from neutral and alkaline solution was attempted, but nothing distilled, demonstrating the absence of acridine, dihydrozcridine, and unchanged diphenylamine. The residue from the steam distillation weighed 5.5 grs. and contained 7.2% nitrogen (micro-Kjeldahl) as compared to 8% calculated for this compound.

The triphenylamine used was of unknown origin. Recrystallized from alcohol it melted at 126° C. and formed no hydrochloride.

Condensation of triphenylamine with formaldehyde.--1.5 grms. of triphenylamine, 10 cc. (excess) of 38% formaldehyde and 20 cc. of conc. hydrochloric acid were refluxed on the steam bath for two hours. The light green product was collected on a filter, washed thoroughly, and dried; it weighed 1.8 grams and did not melt. It was then extracted with hot water, alcohol and ether progressively but still 1.7 grms. of it were recovered. It was not volatile with steam. Its nitrogen content determined by the micro Dumas method was 4.1% and by the micro Kjeldahl method 4.8%.

Nitration of the condensation product.--The condensation product of triphenylamine and formaldehyde was treated with concentrated cold nitric acid (2 grms. in 5 cc.). As it did not dissolve in the cold the mixture was warmed to boiling, whereupon a reaction ensued with evolution of NO_2 . On dilution of the reaction mixture

with water a solid precipitated in amorphous state. It could not be crystallized and darkened perceptibly at 250 C. It contained 14.1% nitrogen, as determined by the micro Dumas method.

Formation of the Haeussermann compound.--1.25 grms. of triphenylamine, 1.7 grms. of benzaldehyde and 20 cc. of concentrated hydrochloric acid were refluxed for two and one-half hours on the steam bath. There was obtained 2.5 grms. of a dark, green, hard, insoluble compound which contained 4.9% of nitrogen as determined by the micro Kjeldahl method.

Conclusion

It is not possible nor safe to draw any conclusion on the basis of the compounds studied. It is, however, apparent that the behavior of these compounds in the presence of the hydrogen halides alone is not at all like that in the Blanc reaction, where zinc halide is also present; nor can the liquid anhydrous halogen acids be compared in strength as condensing agents with sulfuric acid which brings about several of these condensations unsuccessfully attempted with the halogen acids; furthermore, the nature of the substituent groups in the aromatic nucleus is an important factor in the condensations.

Summary

Condensations were attempted with formaldehyde and diphenylmethane, nitrobenzene, and benzene in the presence of hydrogen chloride and bromide.

Condensation of diphenylamine and formaldehyde produced a substituted diphenylmethane.

A complicated nuclear compound was isolated as the main product of the condensation of triphenylamine and formaldehyde, but only a di-substituted triphenylmethane was obtained from the condensation with benzaldehyde.

